UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,408	07/02/2003	Michele Boix	17571 (AP)	4873

7590 08/09/2007

BRENT A. JOHNSON
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
SILVERMAN, ERIC E	
ART UNIT	**PAPER NUMBER**
1615	

MAIL DATE	DELIVERY MODE
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,408	BOIX ET AL.	
	Examiner	Art Unit	
	Eric E. Silverman, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-31 and 40-69* is/are pending in the application.

4a) Of the above claim(s) *22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant is advised that the Examiner assigned to this Application has changed. The Examiner currently assigned to this Application is **Eric Silverman, PhD**, whose contact information can be found at the end of this action. Applicant is further advised that this Application is currently assigned to **Art Unit 1615**.

Applicants' amendment, filed 10/11/2006, has been received. Claims 1 – 5 and 7 – 31 and 40 – 69 are pending in this action. For clarity of the record, it is noted that Applicants' response, on page 11, incorrectly states that claims 1 – 5 and 7 – 69 are pending. Claims 32 – 39 were cancelled by amendment.

Election/Restrictions

Applicants' response confirmed the election of Group I, drawn to a sterile polymeric material and method of administration of said material. Upon review of the prosecution history and Applicants' remarks, it is noted that the Office Action mailed 4/3/2006 incorrectly states that claims 22 – 26 are drawn to a method of administering the particles. Applicants' correctly pointed out that these claims are actually drawn to a method of sterilizing particles. As such, claims 22 – 26 properly belong in non-elected Group II, and are therefore **withdrawn** from consideration.

Applicants' have traversed the restriction requirement on the basis that there is no undue burden to search the claims. This is not found persuasive because the two groups are classified in different classes or subclasses, and thus would require at least different search queries should both groups be searched. The restriction requirement is still deemed proper, and is therefore made **Final**.

Claims 1 – 5, 7 – 21, 27 – 69 are treated on the merits in this action.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawing are of insufficient quality. Figure 1 has poor contrast, some of the text is illegible, and the images, particularly the X 100 images, are either too dark or too light, and thus are unclear. Figures 2 – 4 are graphs, but are of such low quality that the axis labels and scales are not legible, and the plotted data is not visible. In some of these figures, the axis themselves are not visible. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. **The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42 – 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The claims contain the following new matter, which was not disclosed in the application as originally filed.

Claims 42 -- 49 now recite "suspended in an emulsion" which was not disclosed in the original application. Claims 42 – 46 also recite a percentage of microparticles that is not in contact with another microparticle. While the Figure 1 and the expanded figure 1 submitted with the reply do show than many or most of the microparticles are not in contact with another microparticle, it is impossible to determine the percentage of microparticles that are not in contact with another microparticle from these drawings. Thus, this material was not originally disclosed, and is new matter. Claims 47 – 49 recite that 90% of the microparticles do not have more than a specific change in diameter after irradiation. These specific diameter changes are not recited in the originally filed disclosure, nor can they be gleaned from the drawings.

Claims 50 – 67 have the same issues as claims 42 – 49, and in addition, contain new matter for recitation of sterilized materials that need not be irradiated. The originally filed disclosure only contemplates irradiated materials.

Claims 68 and 69 recite a product that has microparticles which are less aggregated than those which are irradiated at 25C. However, the originally filed disclosure only shows a decrease in aggregation when the irradiation step occurs at less than 5 C (see examples in the specification). Thus, these comparison-type limitations are new matter, because it is not commensurate with the comparisons in the original disclosure.

Claims 1 – 5, 7 – 21, and 40 – 69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the microparticles and active agent of shown in the examples of the specification, does not reasonably provide enablement for any other polymeric micrparticle, or the microparticle of the specification in combination with other active agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Enablement is considered in view of the factors enumerated in MPEP 2164.04(a), which serve as a guide to determining whether the experimentation needed by the artisan to make and use the claimed invention is undue. All of these factors have been considered, and the most relevant are discussed in detail below.

- *The breadth of the claims.* Instant claims are drawn to irradiated polymeric materials comprising a plurality of "substantially non-aggregated microparticles", the irradiated "substantially non-aggregated microparticles" microparticles themselves, also sterilized microparticles (which may or may not be irradiated) that are "substantially non-aggregated" (claim 50 and claims dependent therefrom) are included, as are "substantially non-aggregated microparticles" which may or may not be sterilized or irradiated (claim 59 and claims dependent therefrom). With the exception of claims 7 and 8, the microsphere may comprise any polymer. According to claims 7 and 8, the microsphere must comprise either PLGA or PLA, but this may be mixed with any other polymer,

excipients, active agent, or other material. With the exception of claims 13 – 15, any active agent may be present. Claims 13 – 15 limit the active agent somewhat, with claim 15 reading on tazarotene only, but these claims do not limit the nature of the polymeric material, or preclude the incorporation of other active agents, excipients, or other materials. Some of the claims are product by process claims, but the process steps do not limit the scope of the claims, since the same product, when made by another process, would read on these claims. Also note that the term "irradiated" and related terms (irradiate, irradiates, et. cetera) may read on any type of irradiation by any type of wave (sonic, electromagnetic, and so forth) at any frequency.

- *The nature of the invention.* Irradiation with gamma rays s a common, art recognized effective means of sterilizing microspheres that are to be used for medicinal purposes. Applicants have recognized that some microspheres aggregate upon gamma ray irradiation at room temperatures, which is undesirable. Applicants have invented a way of preventing this aggregation in the particular microsphere of the examples by irradiating the microspheres at low temperatures.
- *The level of predictability in the art.* Irradiation ofPLA or PLGA microspheres with gamma rays yields unpredictable results, according to Montanari et al. (cited on PTO 892). See page 318, left column. Montanari shows several examples where similar microspheres are

irradiated, but the results are contradictory. For example, whereas captopril release rates decrease upon irradiation, release rates of progesterone increase. Also, the nature of the drug being used is important. PLA degradation is described to be independent of methadone loading, but higher with increased loading of prometazine, and lower with incorporation of tetracycline. With regard to aggregation, Applicants have alleged that the microparticles of Rodgers and Tice (US 5,534,261 and 4,835,139, respectively) aggregate substantially after irradiation. However, the particles of Montanari, which are made of the same material as that of Rodgers and Tice, do not substantially aggregate upon irradiation, especially upon irradiation under vacuum (see Figure 2, which shows that the particle size distribution in Montanari does not change significantly after irradiation). Furthermore, the presence of a drug alters the effects of irradiation on aggregation. Figure 2 of Montanari shows that without the drug CLO, irradiation causes an overall very small increase in particle size, which indicates some small amount of increased aggregation. However, when CLO is added, the particle size distribution shows a shift towards smaller particles, suggesting that in this case irradiation actually reduced aggregation of the particles (note that aggregation can be correlated to particle size changes because aggregated particles are larger than non-aggregated

particles). Accordingly, the result of irradiation on PLA and PLGA particles is quite unpredictable.

The amount of direction provided by the inventor and the existence of working examples. The working examples only show the effects of irradiation at room temperature and at an undisclosed temperature less than 5 C on one particular microparticle, which contains PLGA and tazarotene and is formed from a solvent evaporation technique. There is no useful information given on what other polymers and drugs combinations would also give the same results. To give an idea of how sparse the teachings of the specification are (outside of the examples, which are instructive but limited in scope) note that of the 14 page specification, 2 pages are background information, a full 4½ pages are merely a long list of drugs (without any comment that addresses how these drugs may interact with PLGA or any other polymeric microsphere), and 3 pages are devoted to the Examples. There is no teaching, or even contemplation, of how to choose a polymer and drug combination that will give the claimed results (lack of aggregation after irradiation)

The amount of experimentation required by the artisan. The artisan who wished to make any aspect of this invention outside of that in the examples would essentially be starting the inventive process from scratch. The artisan would have to choose an active agent and polymer,

from essentially limitless possibilities, make microspheres from this combination (wherein the microspheres may or may not include additional active agents, more than one polymer, and other excipients), and then determine whether or not irradiation actually gives aggregated particles. Given that the art indicates that the results of combining a drug with PLGA is unpredictable, it is even more unpredictable when the polymer is not specified (as in all of instant claims except 7 and 8) and wherein the drug is also not specified (as in all of instant claims except 15). The artisan would have no idea, when starting to make the claimed invention, as to which combinations would actually give non-aggregated particles after irradiation at low temperatures.

Because the art is recognized to be unpredictable, and because the disclosure gives little guidance, the experimentation required by the artisan to make the claimed invention would be similar to that required by one just beginning the path towards making a new invention. At best, the disclosure points the artisan (metaphorically) to a forest without any markings on the trees that might indicate how to pass through. The claims are therefore not fully enabled by the disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 5, 7 – 21, 40 – 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Note that Applicants' arguments regarding the rejections under this statute that were discussed in the Office Action mailed 4/3/2006 are persuasive in view of the amendments. However, the following new grounds of rejection under this statue are necessary at this time.

Independent claims 1 and 59 recite "substantially non-aggregated". The claims do not state, and the specification does not disclose, how little aggregation is allowed for the particles to be "substantially non-aggregated" as claimed. The remaining claims are rejected for depending on one of the abovementioned claims, thereby incorporating the indefinite limitation thereof.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1 – 5, 7 – 12, 16 –21, and 27 – 31 **remain** rejected under 35 U.S.C. 102(b) as being anticipated by US 4,835,139 to Tice et al. for reasons of record and those discussed below. In addition, **newly added claims 40 – 69 are now included in this rejection**. As explained below, the information in Montanari et al. is relied upon as evidence to support this rejection. Applicants' arguments are discussed below.

Claims 1 – 14, 16 – 21 and 27 – 31 **remain** rejected under 35 U.S.C. 102(b) as being anticipated by US 5,534,261 to Rodgers et al. for reasons of record and those discussed below. In addition, **newly added claims 40 – 69 are now included in this**

rejection. As explained below, the information in Montanari et al. is relied upon as evidence to support this rejection. Applicants' arguments are discussed below.

Response to Arguments Against the Anticipation Rejections

Applicants' arguments have been fully considered, but are not persuasive. Applicants' argue that the particles of the art are not "substantially non-aggregated" as required by the claims. Applicants' point to the examples in the specification, which show particular microparticles that are irradiated in at room temperature and at temperatures less than 5C. In these examples, those microparticles irradiated at room temperature are more aggregated than those irradiated at temperatures below 5C. Applicant notes that Rodgers and Tice do not teach irradiation at low temperatures, and thus concludes that the microparticles disclosed in these references must be substantially aggregated. In response, it is noted that the particles of the specification are not the same as the particles of Tice, nor are they the same as those of Rodgers. Therefore more information is required to determine whether or not the results shown in the specification are generally applicable, or if they represent an effect that is only present with the specific particles in those examples. The Montanari et al. reference is useful in this regard. Montanari shows PLGA particles that are irradiated at room temperature (see section 3.1 and Figure 2 – note that in this figure the leftmost "dark" bars relate to unirradiated particles, the center "white" bars relate to particles irradiated in air at room temperature, and the rightmost "grey" bars relate to particles irradiated at room temperature under vacuum; the (A) portion of the figure relates to particles without drug, and the (B) portion relates to particles loaded with drug). The change in

aggregation of the non-drug loaded particles is very small, as evidenced by the fact that there is only about a 10% decrease in the amount of particles in the less than 2 micron size range, and a corresponding small increase in the size of larger particles. This change is even less than 10% when the irradiation is preformed under vacuum. In drug loaded particles, the effect is reversed -- the number of particles in the less than 2 micron size range actually increases slightly (about 7%, as estimated from the graph), whereas that in the larger size ranges decreases.

Montanari therefore shows that the effects noted in the examples of the specification are *not* generally applicable. Rather, these effects appear to be specific to the particular particles of those examples. As such, following Montanari, it is reasonable to conclude that the particles of Rodgers and Tice are actually not substantially aggregated, and thus read on the claimed invention. The burden of proof is now on Applicant to show, for example by a side-by-side comparison, that the particles of Rodgers and Tice are in fact substantially aggregated. Absent such a showing, these rejections are properly maintained.

Claims 1 – 5, 7 – 12, 16 – 21, 27 – 31, and 40 – 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Montanari et al. "Gamma irradiation effects on the stability of poly(lactide-co-glycolide) microspheres containing clonazepam".

The Montanari reference teaches PLGA microspheres containing the active agent clonazepam. These microspheres are irradiated with gamma-radiation, which sterilizes them (section 2.2). According to the referene, the microspheres do not

aggregate to any significant extent upon irradiation (see section 3.1 and Figure 2 – note that in this figure the leftmost "dark" bars relate to unirradiated particles, the center "white" bars relate to particles irradiated in air at room temperature, and the rightmost "grey" bars relate to particles irradiated at room temperature under vacuum; the (A) portion of the figure relates to particles without drug, and the (B) portion relates to particles loaded with drug). The change in aggregation of the non-drug loaded particles is very small, as evidenced by the fact that there is only about a 10% decrease in the amount of particles in the less than 2 micron size range, and a corresponding small increase in the size of larger particles. This change is even less than 10% when the irradiation is preformed under vacuum. In drug loaded particles, the effect is reversed – the number of particles in the less than 2 micron size range actually increases slightly (about 7%, as estimated from the graph), whereas that in the larger size ranges decreases. Thus, the microspheres of Montanari are understood to read on the various aggregation requirements of instant claims.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 15 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,534,261 to Rodgers et al. in view of US 6,365,623 to Perricone for reasons of record and those discussed below.

Response to Arguments Against the Obviousness Rejection

Applicants' arguments have been fully considered, but are not persuasive. Applicants argue that Perricone fails to cure the alleged deficiencies in Rodgers. These supposed deficiencies have been addressed (*vide supra*).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is 571 272 5549. The examiner can normally be reached on Monday to Friday 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571 272 8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric E. Silverman, PhD
Art Unit 1615

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600